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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,223	11/27/2001	Jennifer L. Hillman	PF-0425-1 DIV	4146

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EXAMINER

UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 05/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/996,223

Applicant(s)
Hillman et al

Examiner
Ungar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jul 21, 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2, 11, 17, 18, 20, 23, 26, 27, 30-32, and 34-45 is/are pending in the application.
- 4a) Of the above, claim(s) 11, 20, 23, 26, 27, 30-32, and 34-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 17, and 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(a). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other: _____

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1. The Election filed July 21, 2003 (Paper No. 5) in response to the Office Action of July 2, 2003 (Paper No. 4) is acknowledged and has been entered. Claims 1, 2, 11, 17, 18, 20, 23, 26, 27, 30-32 and 34-45 are pending in the application and Claims 11, 20, 23, 26, 27, 30-32 and 34-45 have been withdrawn from further consideration by the examiner under 37 CAR 1.142(b) as being drawn to non-elected inventions. Claims 1, 2, 17-18 are currently under prosecution.
2. The response (Paper No. 5) to the restriction requirement of July 21, 2003 has been received. Applicant has elected Group I, claims 1, 2, 17-18 for examination with traverse. The traversal is on the ground(s) that Groups 3-6 are all methods of screening and that there would not be an undue burden to examine all of these Groups together. The argument has been considered and the restriction requirement drawn to Groups 3-6 is hereby redrawn as follows: Groups 5 and Group 6 are hereby rejoined to Group 3 as claims 26 and 27 are drawn to an agonist; Groups 5 and 6 are hereby rejoined to Group 4 as claims 26 and 27 are drawn to an antagonist; Group 5 is drawn only to claim 26 as it is neither an agonist nor an antagonist, but rather a binder that is not a modulator. Applicant further argues that Groups 3-6 could be examined together with the composition of matter claims of Group 1 as they are limited in scope to these claims. The argument has been considered but has not been found persuasive because contrary to Applicant's statement, the scope of the claims is not the same. Examiner is willing to revisit the question of rejoining the screening assays with Group 1 upon identification of allowable claims. Applicant's further argue that Groups 9 and 10 are both drawn to preparation of an antibody that are classified identically and therefore could be

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examined together. The argument has been considered but has not been found persuasive because classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and different searches and issues are involved in the examination of each group. Applicant further argues that claims 30-31 have been duplicated in Groups 7 and 8 and that claim 45 is found in both Groups 12 and 13. As drawn to claim 45, it appears that due to an inadvertent typographical error, claim 45 was included in Group 13. Examiner apologizes for any inconvenience and withdraws inclusion of Claim 45 in Group 13. As drawn to Groups 7 and 8, the argument has been considered but has not been found persuasive because Claim 30 as written reads on both *in vivo* and *in vitro* diagnostic methods, which is clearly demonstrated by the inclusion of a humanized antibody in section (e) of claim 31, which are distinct for the reasons of record. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

3. The specification on page 1 should be amended to reflect the status of the parent application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:
"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall

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set forth the best mode contemplated by the inventor of carrying out his invention."

5. Claims 1, 2, 17-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to naturally occurring polypeptides comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1, a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1, a polypeptide having a sequence of SEQ ID NO:1, a composition comprising said polypeptides, wherein the polypeptide has an amino acid sequence of SEQ ID NO:1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

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Furthermore, although drawn to the DNA arts, the findings of the court in *Regents of the University of California v. Eli Lilly & Co* are clearly relevant to the instant rejection. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that “An adequate written description of a DNA...’requires a precise definition, such as by structure, formula, chemical name, or physical properties’, not a mere wish or plan for obtaining the claimed chemical invention”.

The claims as written read on a whole universe of polypeptides that have neither the structure nor the function of SEQ ID NO:1. In particular, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position

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within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. The claimed polypeptides are drawn to molecules comprising "an amino acid sequence" of SEQ ID NO:1, comprising "an amino acid sequence" at least 90% identical to "an amino acid sequence" of SEQ ID NO:1, comprising a biologically active fragment of SEQ ID NO: 1, comprising an immunogenic fragment of a polypeptide having "an amino acid sequence" of SEQ ID NO:1. The claims as written read on polypeptides comprising "an amino acid sequence" of SEQ ID NO:1 wherein the sequence within the polypeptide consists of 2 contiguous amino acid residues of SEQ ID NO:1 which is "an amino acid sequence of SEQ ID NO:1. The claims also

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read on any polypeptide comprising 10 contiguous amino acids of which 9 are contiguous residues of SEQ ID NO:1 which is “an amino acid sequence” of 10 consecutive amino acids. This “amino acid sequence” satisfies the limitation of an amino acid sequence which is at least 90% identical to “an amino acid sequence” of SEQ ID NO:1. The claims also read on any polypeptides comprising 2 or 5 contiguous amino acids of SEQ ID NO:1 (that is those with biologically active fragments or immunogenic fragments). Although Bowie et al, Burgess et al and Lazar et al teach the unpredictability of the effect of the change of even a single amino acid in a polypeptide, given that SEQ ID NO:1 consists of 446 amino acids, the fact pattern here multiplies that unpredictability in that there can be up to 444 changes in amino acids wherein polypeptide species have neither the structure nor the function of SEQ ID NO:1. Thus, the claims as written read on a whole universe of undefined polypeptides which are not described in the specification.

The instant disclosure of a single species of polypeptide does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. The fact pattern here is similar to that of *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) in that while a whole universe of molecules is claimed, only a single sequence has been disclosed, therefore *Regents of the University of California v. Eli Lilly & Co* is also applicable to the claims at issue here. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus

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claimed. The specification proposes to discover other members of the genus by using screening methods. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the claims. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristic or property of the instant polynucleotides is provided in the claims such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, and because the genus is highly variant, the disclosure of a single specific polypeptide sequence and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

6. Claims 1, 2 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising SEQ ID NO:1 and a composition thereof, does not reasonably provide enablement for a naturally occurring polypeptides comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1, a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID

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NO:1, a polypeptide having a sequence of SEQ ID NO:1, a composition comprising said polypeptides, wherein the polypeptide has an amino acid sequence of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to naturally occurring polypeptides comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1, a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1, a polypeptide having a sequence of SEQ ID NO:1, a composition comprising said polypeptides, wherein the polypeptide has an amino acid sequence of SEQ ID NO:1. This includes polypeptides comprising “an amino acid sequence” of SEQ ID NO:1 wherein the sequence within the polypeptide is consists of 2 contiguous amino acid residues of SEQ ID NO:1 which is “an amino acid sequence of SEQ ID NO:1. The claims also read on any polypeptide comprising 10 contiguous amino acids of which 9 are contiguous residues of SEQ ID NO:1 which is “an amino acid sequence” of 10 consecutive amino acids. This “amino acid sequence” satisfies the limitation of an amino acid sequence which is at least 90% identical to “an amino acid sequence” of SEQ ID NO:1. The claims also read on any polypeptides comprising 2 or 5 contiguous amino acids of SEQ ID NO:1 (that is those with biologically active fragments or immunogenic fragments). The claims also read on biologically active fragments and immunogenic fragments of polypeptides wherein those fragments are not limited to

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biological activity or immunogenicity of SEQ ID NO:1 since those fragments are found in polypeptides having an “an amino acid sequence” of SEQ ID NO:1, but there is no requirement that those immunogenic or biologically active fragments consist of a sequence found in SEQ ID NO:1. One cannot extrapolate the teaching of the specification to the scope of the claims because as set forth above, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein’s sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in

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Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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8. Claims 1, 2, 17-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Evans et al (Biochemistry, 1988, 27:4680-4686, IDS item 11) and see also Sequence Search listing US 09-996-223-1.rpr, result 1, attached hereto.

The claims are drawn to an isolated polypeptide comprising naturally occurring polypeptides comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1, a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1, an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1, a polypeptide having a sequence of SEQ ID NO:1, a composition comprising said polypeptides in a pharmaceutically acceptable excipient, wherein the polypeptide has an amino acid sequence of SEQ ID NO:1.

Evans et al teach an isolated, naturally occurring polypeptide sequence with 96.1% identity to 96% of SEQ ID NO:1, that is 92.2% identity to the entire molecule, wherein the polypeptide of the prior art reference comprises an amino acid sequence of SEQ ID NO:1 and comprises both biologically active fragments and immunogenic fragments (see Sequence Search listing US 08-970-134-2.rge, result 1). Further, Evans et al teach an expression vector containing at least a fragment of SEQ ID NO: 2, a host cell containing the expression vector and a method for producing a polypeptide comprising the amino acid sequence of a fragment of SEQ ID NO: 1 (see Abstract) wherein the produced polypeptide is in a pharmaceutically acceptable excipient. All of the limitations of the claims are met.

9. No claims allowed.

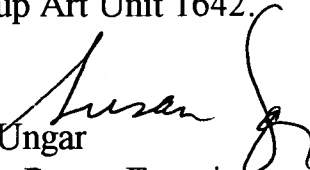
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10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.


Susan Ungar
Primary Patent Examiner
September 11, 2003